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Enantiomeric Conformations of 5-Acyl-2-Oxo-2H-1,3,4,5- Tetrahydrobenzodiazepines

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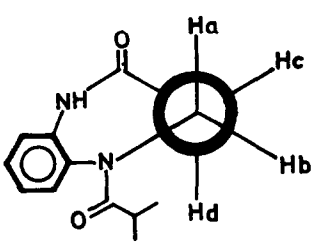
Abstract : 5-Acyl-2-oxo-2H-1,3,4,5-Tetrahydrobenzodiazepines exist in slowly interconverting pair of enantiomeric conformations detectable by NMR at ambient temperature.

2-Oxo-2H-1,3,4,5-tetrahydro-1,5-benzodiazepines (THBD) form an important subclass of the pharmacologically preeminent 1,5-benzodiazepines[1]. We report, for the first time, in this paper that 5-acyl THBDs exist in enantiomeric conformations. We also describe how the gem dimethyl substituents on the diazepine ring and the bulkiness of the acyl substituent on N-5 affect the stability of these conformers. Our studies reveal that judicious variation of substituents on the ring and the acyl side chain render the ring enantiomeric conformations so stable as to be directly detectable by ^{1}H NMR even at room temperature. These studies assume importance especially in view of the recent results which point out enantiomer specific pharmacological activity of acyldibenzodiazepinones[2].

The 60 MHz ^{1}H NMR data at ambient temperature (Table) indicate that THBDs I to III exist as a rapidly interconverting enantiomeric pair of conformers A and B (Figure 2). However, THBD (IV), an acetyl derivative of I, exists as a slowly interconverting pair of enantiomeric conformations A and B (two broad signals for the C-4 methylene hydrogens appear at δ 3.5 and 4.9, each integrating for one proton, see Table). The ^{13}C NMR of IV at ambient temperature showed neither broadening nor multiplicity for any of its carbon signals (See Table, footnote c). This observation in conjunction



J Values in Hz

H_a-H_b	12.7
H_a-H_c	5.7
H_a-H_d	12.7
H_b-H_c	3.0
H_b-H_d	6.6
H_c-H_d	13.0

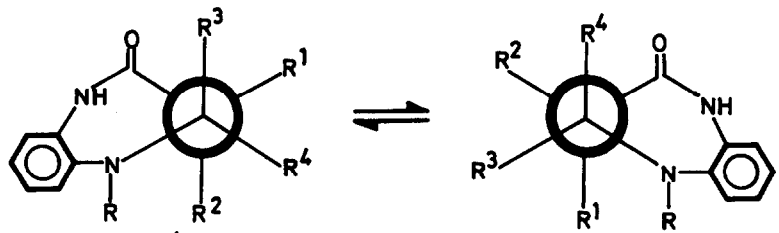
FIGURE.1 CONFORMATION OF THBD VII

with geminal non equivalence of C-4 protons (see above) and C-3 protons observed in the proton NMR spectrum shows the existence of slowly interconverting enantiomeric conformations A and B. Very interestingly ^{1}H NMR of the dimethyl analogues of IV, namely V & VI, disclosed that V existed as a rapidly interconverting pair of conformers A and B whereas VI existed as a pair of stable conformers A and B with sharp signals at ambient temperature. (Table)

The ambient temperature ^{1}H NMR at 300 MHz for VII was amenable to first order analysis. The coupling data shown in Figure 1 is indicative of a staggered ethane arrangement about the C_3-C_4 bond. Similar conclusions could be arrived at from the ^{1}H NMR spectrum of IV at 300 MHz whose resonances were considerably broadened showing faster interconversion of A and B compared to VII.

From the temperature dependent ^{1}H NMR spectra at 300 MHz, (using coalescence temperature method), the $\Delta G^{\neq}$ (barriers to conformer interconversion) for V and VIII (the latter has a bulkier acyl side chain than in V) were found to be 14.0 K cal/mol ($T_c = 314^oK$) and 15.8 K cal/mol ($T_c = 318^oK$) respectively. A lower limit for the barrier for VI is estimated to be 14.8 K cal/mol (at 300^{o}K) from its ambient temperature NMR spectrum.

Thus our studies disclose (a) acyl THBDs interconvert slowly between the enantiomeric conformations A and B, unlike their parent THBDs I to III. This presumably arises from the interference



S.No.	R	R^1	R^2	R^3	R^4
I	H	H	H	H	H
II	H	CH_3	CH_3	H	H
III	H	H	H	CH_3	CH_3
IV	$COCH_3$	H	H	H	H
V	$COCH_3$	CH_3	CH_3	H	H
VI	$COCH_3$	H	H	CH_3	CH_3
VII	$COCH(CH_3)_2$	H	H	H	H
VIII	$COCH(CH_3)_2$	CH_3	CH_3	H	H

FIGURE. 2 CONFORMATIONAL INTERCONVERSIONS OF BENZODIAZEPINONES

TABLE : Physical and proton NMR Data[a] on Tetrahydrobenzodiazepinones[b]

No.	mp °C	^{1}H NMR Data (Solvent)
I	144-146	($CDCl_3$): 2.72 (t, 2H, -$C^3\underline{H}_2$, J = 6.1 Hz); 3.66 (t, 2H, -$C^4\underline{H}_2$, J = 6.1 Hz); 3.80 (s, 1H, N$\underline{H}$), 6.67-7.07 (m, 4H, arom.); 7.92 (s, br, 1H, -N$\underline{H}$-CO).
II	185-195	(DMSO-d_6 + $CDCl_3$ + D_2O to remove N$\underline{H}$ couplings); 1.30 [s, 6H, $C^3(C\underline{H}_3)_2$]; 3.04 (s, 2H, -$C^4\underline{H}_2$); 6.50-7.00 (m, 4H, arom.)
III	260-262	(DMSO-D_6): 1.24 [s, 6H, $C^4(C\underline{H}_3)_2$]; 2.21 (s, 2H, $C^3\underline{H}_2$); 4.70 (s, 1H, -N$\underline{H}$); 6.80-7.00 (m, 4H, arom.); 9.45 (s, 1H, -N$\underline{H}$-CO)
IV	137	($CDCl_3$): 1.85 (s, 3H, $COC\underline{H}_3$); 2.60 (m, 2H, $C^3\underline{H}_2$); 3.50 (m, br, 1H, $C^4\underline{H}$, R^4 in A & R^3 in B); 4.90 (m, br, 1H, $C^4\underline{H}$, R^3 in A & R^4 in B); 7.00-7.60 (m, 4H, arom.); 9.40 (s, 1H, -N$\underline{H}$-CO)
V	197-199	($CDCl_3$): 1.30 [s, 6H, $C^3(C\underline{H}_3)_2$]; 2.05 (s, 3H, -$COC\underline{H}_3$); 3.85 (s, br, 2H, $C^4\underline{H}_2$); 7.00-7.30 (m, 4H, arom.); 9.45 (s, 1H-N$\underline{H}$-CO).
VI	213	($CDCl_3$): 1.46 (s, 3H, C^4-$C\underline{H}_3$); 1.64 (s, 3H, -$COC\underline{H}_3$); 1.93 (s, 3H, C^4-$C\underline{H}_3$); 2.10 (d of AB quartet, 1H, J = 13 Hz, $C^3\underline{H}$); 2.55 (d of AB quartet, 1H, J = 13 Hz, $C^3\underline{H}$); 6.91-7.54 (m, 4H, arom.); 10.50 (s, 1H, N$\underline{H}$-CO).
VII	179-183	($CDCl_3$): 0.87 [d, 3H, -COCH($C\underline{H}_3$), J = 6.5 Hz]; 1.10 [d, 3H, COCH($C\underline{H}_3$), J = 6.5 Hz]; 2.28-2.74 (m, 3H, $C^3\underline{H}_2$); 3.26-3.65 (m, br, 1H, $C^4\underline{H}$, R^4 in A & R^3 in B); 4.70-5.20 (m, br, 1H, $C^4\underline{H}$, R^3 in A & R^4 in B); 7.05-7.47 (m, 4H, arom.); 9.33 (s, 1H, -N$\underline{H}$-CO).
VIII	160-162	($CDCl_3$): 0.66-1.55 [m, br, 12H, $C^3(C\underline{H}_3)_2$ & -COCH($C\underline{H}_3$)$_2$]; 2.55-3.20 [m, 2H, -COC$\underline{H}$(CH_3)$_2$ & $C^4\underline{H}$, R^4 in A & R^3 in B]; 4.80 (d, br, J = 12 Hz, 1H, $C^4\underline{H}$, R^3 in A and R^4 in B); 6.90-7.40 (m, 4H, arom.); 9.40 (s, 1H, -N$\underline{H}$-CO).

[a] All ^{1}H NMR data in this Table were taken at ca. 24°C with TMS as internal standard in Varian or Hitachi spectrometers operating at 60 MHz. [b] Satisfactory elemental analyses were obtained for all new compounds. [c] C-13 NMR data(ambient temperature spectra at 22.6 MHz, TMS internal standard, OFR multiplicities in parentheses): For IV, 22.6(q), 33.6(t), 47.1(t), 122.8(d), 125.9(d), 129.2(d), 129.6(d), 134.0(s), 136.3(s), 170.4(s), 173.5(s); For VII, 19.6(q), 31.5(d), 33.7(t), 47.0(t), 123.0(d), 126.0(d), 129.1(d), 129.3(d), 134.0(s), 136.6(s), 173.5(s), 177.6(s). A slight broadening of only the diastereotopic methyl signals at δ 19.6 was observed.

of the acyl group with aromatic C_6-H bond and also with C_4 substituents in the transition state of the ring inversion; (b) increase of the bulk of the acyl side chain increases the barrier: V vs VIII (vide infra). (c) Substituents at C-4 interfere with the acyl side chain in the transition state increasing the barrier whereas substituents at C-3 position increase the energy of the ground state conformation decreasing the barrier. This conclusion is getting confirmation from the fact that at ambient temperature, equilibration between conformers A and B of THBD V is faster than similar equilibration of THBDs IV and VI (compare ambient temp ^{1}H NMR Table). We attribute this to destabilizing 1,3-steric interactions between the N-acetyl group and one of the C-3 methyl groups in the ground state conformation of V.

Further ramifications of these observations are under investigation.

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